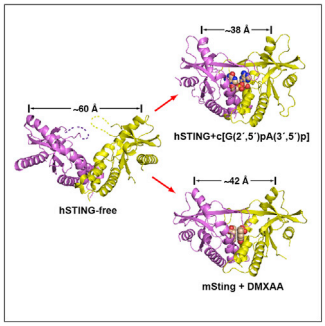
In This Issue

Cell



2′5′s Company, 3′5′s a Crowd

PAGE 748

Gao et al. investigate the underlying principles that determine recognition and binding of the human and mouse immune signaling protein STING by second messenger cGAMP linkage isomers. Cellular assays establish 2′,5′-containing isomers as more specific triggers of the interferon pathway compared to all 3′,5′-containing isomers. Their findings also highlight the importance of a specific serine in human STING in determining sensitivity to the antiviral and antitumorigenic drug DMXAA.

Kick Start for a Kinase

PAGE 737

Small-molecule therapeutics targeting disease-related enzymes typically inhibit the activity of these proteins. Hertz et al. find that an ATP analog increases the activity of PINK1, a kinase mutated in some cases of Parkinson's disease, and ameliorates neuronal phenotypes caused by reduced PINK1 function. The approach may offer a new modality for drug discovery.

Viral Origami for Multifunctionality

PAGE 763

Viruses encode so few proteins that it's common for one viral protein to have multiple functions. Bornholdt et al. elucidate the structural basis of the multifunctionality of Ebola virus VP40 through multiple crystal structures, biochemistry, and microscopy. A VP40 dimer traffics to the cellular membrane, a rearranged linear hexamer fabricates and buds new virions, and a ring-like RNA-binding structure controls transcription inside infected cells. The results demonstrate how an unmodified polypeptide rearranges to extend its functional repertoire.

Polymerase Unpacked

PAGE 775

Braberg et al. develop an approach that enables genetic interrogation of point mutants of multifunctional proteins and apply it to yeast RNA polymerase II. The detailed analyses link specific regions of the complex with distinct functions, allow classification of mutants affecting transcription rates, and reveal layers of integration between RNAP II and pre-mRNA splicing. This general method opens the way for characterization of other complex cellular machines and assemblies.

Filtering Fluctuations for Fidelity of Form

PAGE 789

Specification of gene expression programs during axis patterning in *Drosophila* embryos occurs in a strictly controlled manner. Using single-molecule quantification, Little et al. show that despite inherently stochastic transcription in embryos, the resulting output of completed transcripts for early patterning genes is highly precise. Precision arises from simple accumulation and distribution of transcripts between mitotic cycles, minimizing the fluctuations due to universally stochastic gene expression.

A Cohesin Bookmark for Transcription Factor Binding

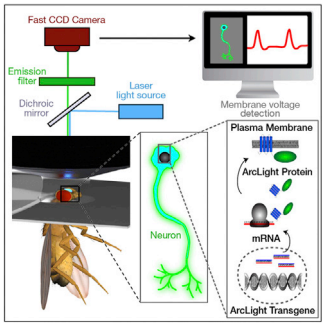
PAGE 801

By analyzing the binding sites of over 100 transcription factors (TFs) in two human colon cancer cell lines, Yan et al. report that the majority of TF binding occurs around cohesin sites within a small fraction of genome (<1%) and that cohesin binding increases local DNA accessibility. Cohesin remains bound after TFs are evicted in early M phase, suggesting that cohesin may promote re-establishment of TF clusters after DNA replication.

DNA Landscape Maps Location in Fate and Time

PAGE 888

Stergachis et al. detect striking patterns in the gain and loss of DNaseI hypersensitive sites (DHSs) as cellular development progresses from ESCs through to terminally differentiated cells. These DHS patterns alone can convey information about cell fate and lineage relationships in development that is distinct from information derived from gene expression. Conversely, in tumor cells, the DHS landscape indicates disordered activation of primitive DHSs that distorts normal lineage relationships.



Visualizing Voltage in Neural Circuits

PAGE 904

Methods to monitor the membrane potential of multiple genetically targeted neurons in intact neural circuits are highly desirable because they offer numerous advantages over electrophysiological recordings. Cao et al. show that the genetically encoded fluorescent voltage indicator "ArcLight" robustly reports electrical events in genetically targeted neurons in the *Drosophila* fly brain. The reported approach enables optical measurement of membrane potential, the key cellular parameter that underlies neuronal information processing, in intact neural circuits.

Pipeline for RNA Processing

PAGE 814

The Ski complex functionally supports the eukaryotic RNA-degrading exosome complex. Crystallographic and biochemical analyses from Halbach et al. show that the Ski complex comprises an ATPase base and a regulatory lid that controls access of RNAs to the helicase subunit Ski2. The exosome and Ski complexes form a channel that connects their helicase and nuclease activities, creating a direct pipeline for mRNP remodeling and degradation.

Repair Kit for Heart

PAGE 827

Identification of cell populations capable of regenerating adult mammalian cardiac cells have been the subject of intensive research. Ellison et al. employ a number of approaches and injury models to provide evidence that c-kit-positive cardiac cells restore cardiac function by regenerating lost cardiomyocytes. Ablation of these cells abolishes regeneration and recovery that can then be rescued by injecting c-kit-positive cells. Thus, the authors provide strong evidence for the necessity and sufficiency of one cardiac cell population driving regeneration.

The A to Z of DCs

PAGE 843

Macrophages and dendritic cells (DCs) are generally distinguished by phenotypic and functional characteristics. However, these often overlap, making it difficult to separate the two cell types and assess whether they perform unique functions in immunity and homeostasis. Schraml et al. describe the first in vivo model for fate mapping the provenance of DCs in mice and reveal that in some tissues, cells previously thought to be monocytes/macrophages are in fact descendants from DC precursors.

Taking the TORC out of Stress

PAGE 859

mTORC1 controls growth and survival in response to metabolic cues. Thedieck et al. show that upon cellular stress, astrin, a protein frequently upregulated in tumors, inhibits mTORC1 association and recruits the mTORC1 component raptor to stress granules, preventing mTORC1 hyperactivation and apoptosis. Astrin is required for the suppression of apoptosis in cancer cells during stress, suggesting that targeting astrin could sensitize tumors to apoptosis.

Leveraging Nascent Allostery

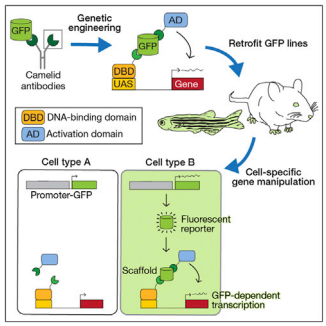
PAGE 875

Allosteric regulation requires not only the evolution of an allosteric activator but also the capacity of the target protein to be allosterically regulated. Taking advantage of species divergence in the allosteric regulation of a MAPK in budding yeast by the scaffold Ste5, Coyle et al. find that a latent capacity for allosteric regulation is present in MAP kinases present in species that diverged before the appearance of Ste5. This suggests that such regulation can evolve by leveraging substrates' pre-existing dynamic properties.

TRIP to Chromatin Neighborhoods

PAGE 914

Reporter genes integrated into the genome can reveal how local chromatin context affects transcription and other functions. Akhtar et al. present a method to map and monitor Thousands of Reporters Integrated in Parallel (TRIP). This yields genome-wide maps that link chromatin composition and structure to gene expression and other functions. The design of the reporters is highly flexible and enables the probing of chromatin effects on a variety of regulatory processes.



GFP Builds Bridges

PAGE 928

Tang et al. extend the utility of GFP by developing it as a scaffold for control of different biological activities. Recognition of GFP by nanobodies induces formation of a transcription factor from split components. Cell-specific control of expression is tunable, opening up any transgenic GFP cell line or animal for cell-specific gene manipulation.